REMARKS

Claim Amendments

New dependent method of treatment claims have been added by the above amendments. Specifically:

New claim 7 is dependent on claim 2, and further defines the cancer as a non-small cell lung cancer (NSCLC). Support for this claim is found in the specification, *inter alia*, at page 5, line 29.

New claim 8 is dependent on claim 3, and further defines the tumour as a tumour of the colon, breast, prostate, lungs or skin. Support for this claim is found in the specification, *inter alia*, at page 6, lines 2-3.

Claim Rejections - 35 USC § 103

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin *et al.* (WO 01/32651) in view of Gorski *et al.* This ground for rejection is respectfully traversed.

The Examiner notes that claims 1-3 are drawn to a method for the treatment of cancer and a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, which comprises administering ZD6474 with an effective amount of ionizing radiation.

In formulating this rejection, the Examiner asserts that WO 01/32651 discloses a method for the treatment of cancer (in particular solid tumors, citing page 28, lines 11-17), and a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal (citing page 26, lines 10-14), which method comprises administering a compound of formula I as generically described beginning on page 3 of the reference. The Examiner further notes that ZD6474 is specifically identified as a compound of Formula I (citing claim 8). The Examiner then asserts that WO 01/32651 teaches that this treatment may additionally include radiotherapy administered simultaneously, sequentially or separately, citing page 26, lines 22-30 of this reference. From these observations the Examiner concludes:

> Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to use ZD6474 with concurrent radiotherapy in the treatment of cancer and in the production of an antiangiogenic and/or vascular permeability

> reducing effect in a warm-blooded animal, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

(Action at pages 2-3).

The Examiner acknowledges that Applicant's data at pages 22-24 of the present specification displays synergism between ZD6474 and sequential radiation therapy. However, he asserts that the prior art indicates that this synergistic effect is expected, citing Gorski *et al.* Gorski *et al.* is said to teach "that VEGF inhibitors, a class of compounds of which ZD6474 is a member, administered with ionizing radiation results in greater than additive antitumor effects," citing page 3378, paragraph 1 of the Gorski *et al.* reference.

This rejection is respectfully traversed.

At page 3 of the present disclosure Applicants specifically acknowledge the disclosure of page 26 of WO 01/32651, now cited by the Examiner, noting that:

> In WO 01/32651 it is stated that compounds of that invention: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment,"

and that WO 01/32651 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and chemotherapy. In fact WO 01/32651 expands upon the conjoint chemotherapy treatment, describing at page 27, lines 1-30, five main categories of therapeutic agent including (i) a number other types of antiangiogenic agents; (ii) a number of different cytostatic agents; (iii) biological response modifiers; (iv) antibodies; and (v) a variety of antiproliferative/antineoplastic drugs and combinations thereof.

Moreover, the compound that is ZD6474 is just one of a number of compounds that are within the scope of the WO 01/32651 disclosure or described therein and, as noted above, WO 01/32651 also describes a number of different conjoint treatments/therapies with which any of the compounds of WO 01/32651 may be combined. Radiotherapy is just one of the many possible described treatments that can be used with any of such compounds. Thus, in order to achieve the presently claimed invention, one first has to select one particular compound (ZD6474) from the many disclosed in WO 01/32651 and then select one type of other treatment (radiotherapy) from the many disclosed, to use in combination.

Moreover, nowhere in WO 01/32651 does it state that the use of any compound of formula (I) with any of such conjoint treatments will produce surprisingly beneficial effects, no less that any particular combination might be surprisingly beneficial. However, as stated at page 3 of the present specification:

> Unexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection of the combination therapies listed in WO 01/32651, namely with ionising radiation, produces significantly better effects than any one of ZD6474 and ionising radiation used alone.

This statement is backed up with data that demonstrates this surprisingly beneficial effect that is achieved by the use of ZD6474 in combination with ionising radiation. Thus, the data in Table 1 at page 22 of the present specification show:

> ... that in each case (5Gy or 3 x 2Gy experiments) the combination of radiation plus ZD6474 provided a better therapeutic effect than either therapy alone.

The data in Table 2 at page 23 show:

> ... that 50 mg/kg dose of ZD6474 combined with 3 x 2 Gy radiation treatment gave a growth delay that was significantly greater than that of either single treatment alone.

The description on page 24 of the present specification goes on to conclude:

> The antitumour effect produced by sequential combination treatment with 3 x 2 Gy radiation and 50 mg/kg ZD6474 <u>was greater than the sum of the growth delays induced by the individual therapies</u>, and comparable to treatment with 5 x 2 Gy of radiation alone.

(emphasis added). Thus synergy achieved by the presently claimed invention has clearly been demonstrated.

It should be noted that if 3 x 2 Gy radiation and 50 mg/kg ZD6474 is comparable to 5 x 2 Gy radiation, this is synergistic because it has been possible to reduce the dose of radiation while maintaining the anti-tumour effect. This is discussed in the definition of synergy in the present specification at pages 6-7, where it is said:

> ... the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component is dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment.

Although acknowledging this showing of synergistic effect at page 3 of the Action, the Examiner asserts that the prior art indicates that this synergistic effect is expected, citing Gorski *et al.* Specifically, the Examiner asserts that Gorski *et al.* "teaches that VEGF inhibitors, a class of compounds of which ZD6474 is a member, administered with ionizing radiation results in greater than additive antitumor effects," citing page 3378, paragraph 1 of the Gorski *et al.* reference. It is respectfully submitted, however, that this broad generalization does not follow from the actual disclosure of Gorski *et al.*

Gorski *et al.* in fact describes the use of ionising radiation with an anti-VEGF (vascular endothelial growth factor) *antibody* in a number of mouse xenograft models. The anti-VEGF antibody binds to free VEGF ligand which is then not available to bind to the VEGF receptor. Thus the anti-VEGF antibody does not act as an inhibitor of the VEGF receptor directly. Conversely ZD6474 is a VEGF receptor tyrosine kinase inhibitor that is an anilinoquinazoline namely:

> 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline.

ZD6474 binds to the intracellular tyrosine kinase domain of the VEGF receptor and thus acts at a different point in the VEGF signalling pathway. The profile of activity of ZD6474, being a small molecule tyrosine kinase inhibitor that acts intracellularly, will be different to that of a VEGF antibody that binds VEGF extracellularly. Given the different structures, modes of actions and profiles of inhibitory activity of the anti-VEGF antibodies described in Gorski *et al.* versus ZD6474, it would not have been possible to make any reliable prediction of what results a combination of ZD6474 with ionising radiation would give compared to a combination of an anti-VEGF antibody with ionising radiation based on the disclosure in Gorski *et al.*

Thus it is respectfully submitted that the presently claimed invention, which is directed toward a combination of ZD6474 and ionising radiation, is not rendered *prima facie* obvious by the disclosure of WO 01/32651 because there is no suggestion or teaching within WO 01/32651 that would lead the skilled person to select ZD6474 out of the many compounds of formula (I) and combine it with radiotherapy, which is only one of many disclosed conjoint treatments. Nevertheless, *even if* one were to somehow make this combination out of the disclosure of WO 01/32651, present Applicants have demonstrated with data included in their specification that

this presently claimed combination unexpectedly yields a particularly advantageous, synergistic result, thereby overcoming any *prima facie* obviousness that might be asserted.

The unexpected or surprising nature of this synergistic result *is not diminished* by the disclosure of Gorski *et al*, in that ZD6474, as a VEGF receptor tyrosine kinase inhibitor, has a different mode of action and profile of activity than the anti-VEGF antibody described in Gorski *et al*. Therefore, the demonstrated synergistic results of the combination of ZD6474 and ionising radiation could not have been predicted from the disclosure of WO 01/32651 and/or in view of Gorski *et al*. Accordingly, this ground for rejection should be withdrawn.

Conclusion

All grounds for rejection having been addressed above and, it is believed, overcome, all claims are now in condition for allowance and a Notice to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

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